Profile of Gene E. Robinson

Most researchers may not adhere to E. O. Wilson's sentiments, "Love the organisms for themselves first, then strain for general explanations, and, with good fortune, discoveries will follow. If they don't, the love and the pleasure will have been enough." Instead, many researchers choose to follow a particular question as their passion and then select the most appropriate organism with which to work. But one scientist who fits Wilson's sentiment is Gene Robinson, the G. William Arends Professor of Integrative Biology in the Department of Entomology at the University of Illinois at Urbana–Champaign and one of the world's foremost experts on the honey bee. In only one day, Robinson became smitten with these social insects and their mesmerizing combination of order and chaos. In the years since, he has devoted his research to uncovering the mechanisms that govern honey bee society, which rivals human society in terms of complexity and cohesion, and has focused principally on discerning how bees control their system of organized yet flexible division of labor.

Fortunately, Robinson will not have to settle for the beauty of bees as his only reward because bees have proven to be a wonderful model system. "They're great because you can easily see how social behavior is influenced by environmental factors, such as removing all the foragers and seeing how the rest of the colony adapts," says Robinson. "You can also see genetic influences, how bees of different genotypes do things different ways." Through Robinson's research, many of the hormones, neurochemicals, brain pathways, and environmental cues that determine how bees transition from hive housekeepers to food gatherers are now known. Robinson, who was elected to the National Academy of Sciences in 2005, is pursuing the genetic factors at work in division of labor, examining the interplay between gene expression and behavior. As he describes in his Inaugural Article in this issue of PNAS (1), hive bees and foragers differ in approximately 40% of their brain gene expression, changes that occur in two principal shifts and are influenced by hereditary, environmental, and physiological effects.

Gene E. Robinson

Stung with a Passion

Robinson was 18 years old when he first experienced the wonders of bees. He had taken time off from his undergraduate studies at the State University of New York (Buffalo, NY) to travel to Israel and work on a kibbutz (communal farm). "One day while I was working, they asked if someone would just help out with the bees temporarily," he says, "and since I was bored to tears picking grapefruits, I volunteered. I remember I was smitten that very first day." He then wrote a letter to his parents informing them that he fell in love with honey bees and wanted to work with them for the rest of his life. "They were suitably shocked and thought, 'No doctor, no lawyer, where did we go wrong?'" he says, "but then after a series of exchanges, my mother finally said, 'Well, as long as you found something that makes you happy. Just be sure to get a Ph.D. in it!'"

Robinson did not have to venture far from home to fulfill his mother's wishes; he returned to the United States and his undergraduate studies and entered Cornell University (Ithaca, NY). He majored in biology with an emphasis on entomology. "[Entomology] was something I had never heard of, actually, as a city kid growing up in Buffalo," he says. After completion of his bachelor's degree in 1977, Robinson was unsure whether he should pursue bee biology in graduate school, so he spent a couple of years working in the bee industry, as an apiary inspector in New York state, a queen breeder in California, and a beekeeping trainer for a rural development program in Colombia. There, he decided he wanted to continue his research on bee biology. "I was smitten with honey bees in a passionate but immature and uneducated way," Robinson says, "so I enrolled in the Cornell entomology department to change my perspective and understand bees as insects and representatives of a phenomenon called an insect society."

He joined the laboratory of Roger Morse, which was a good fit because Robinson still had a broad and unrefined interest in bees. At the time, Morse's laboratory worked on a number of different projects, which "provided a great deal of exposure and independence," says Robinson. In 1982, he completed his master's degree with a project on how worker bees treat a foreign queen introduced to their hive. Although he did not find the project highly interesting, he found it valuable in helping him understand how to frame a scientific question properly. "Anyone can ask a good question. Kids are incredibly curious and ask all sorts of great questions," Robinson says, "but is it a question that's framed so you can move forward answering a piece of it one way or the other?"

For his doctoral research, Robinson remained at Cornell and made his first foray into the division-of-labor system in honey bees. "Basically, an adult worker bee lives about 5–6 weeks, and she spends the first half doing a series of jobs in the hive, short careers if you will, and then she makes a major career transition to being a forager at about 3 weeks. This is an individual process of behavioral maturation that at the colony level gives rise to division of labor," explains Robinson. The behavioral aspects of that system were already well known, first described by Aristotle, but mechanistic analyses had not yet been done. Some research hinted that hormones were involved, and Robinson saw this area as a promising line of study, especially because he was working closely with Henry Hagedorn, an insect endocrinologist. "Morse gave me the freedom to learn from my own mistakes and become independent, but I also benefited greatly from the more hands-on mentoring that Hagedorn generously and graciously provided me, even though he was not my official advisor," says Robinson.

A Bee Street Journal?

While working specifically on the effects of the compound juvenile hormone on foraging and flight activity (2, 3), Robinson surmised that studying division of

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 16068.

labor and bee behavioral endocrinology at different biological levels could provide a lifetime of work. "I had started the endocrine approach," he says, "and I thought, 'Well, what's known about how the brain is changing to support these different activities? What's going on neurochemically? How might we address these kinds of issues?'" Robinson was unsure whether this area was a viable research direction, so to obtain some feedback, he consulted another Cornell faculty member, Ron Hoy. Hoy encouraged Robinson and put him in touch with John Hildebrand, a professor at Columbia University (New York, NY) who used a similar, integrative approach in the study of moth olfaction.

"John also turned out to be extremely encouraging and that gave me the confidence to start planning my future," says Robinson. Robinson felt he needed to go in two different directions: neurobiology and genetics. After finishing his Ph.D. in entomology in 1986, he decided to focus on genetics. He joined Robert Page's group at Ohio State University (Columbus, OH) as a postdoctoral researcher, where he began probing the genetic basis for division of labor in bees. "At that time, the prevailing assumption was that the differences between bees were either environmental or developmental," he says. Robinson looked at corpse removal among bees, a specialized function that only a few bees in each colony performed. He found that indeed a genetic component influenced a bee's chance of becoming an undertaker (4). However, a specific genotype was not rigidly associated with corpse removal. "It was much more of a subtle effect," Robinson says, "which is exactly what you would expect in a complex society."

After 3 years at Ohio State, Robinson joined the faculty of the entomology department at the University of Illinois. He continued both his hormonal and genetic variation studies but also began studying the social aspects of division of labor. "The honey bee system is in fact very flexible. They can accelerate, delay, or even reverse their maturation depending on the needs of the colony," Robinson explains. How such changes are regulated was particularly interesting to him because social insects operate under a complex system where a higher-level entity, the colony, makes decisions, but no individual, not even the queen, is in charge. "So, how does a colony reallocate its labor in the face of changing conditions, when we don't expect there to be an executive committee or '*Wall Street Journal*' telling the workers what the labor market is like?" he asks.

Along with Zachary Huang, his first postdoctoral associate, Robinson reared bees in differently sized groups and found that chemical interactions between workers were significant, particularly an inhibitory influence from older to younger bees that delayed the young bees' onset of maturation (5). Years later, Robinson collaborated with colleague Yves LeConte and found that the substance involved was the primer pheromone ethyl oleate (6). In between these findings, Robinson had uncovered other pheromones that contributed to maintaining the high plasticity of the honey bee labor system, including one produced by the brood, and another, mandibular pheromone, produced by the queen (7, 8).

"OK, this is the marriage that needs to be made—genomics and social behavior."

Wishing to employ the two-pronged research approach he had envisioned in graduate school, Robinson initiated studies in the 1990s on the neurobiology of division of labor. He teamed with Susan Fahrbach, another faculty member of the University of Illinois entomology department. Trained as a neurobiologist, Fahrbach provided an excellent complement to Robinson's behavioral and genetic expertise. Together they began a study examining changes in brain structure during behavioral maturation. Their first major finding uncovered that a part of the bee brain region known as the mushroom body, important for learning and memory, was larger in forager bees than hive bees. (9). "Since then, we have been studying various aspects of mushroom body plasticity, understanding the mechanisms underlying it and the possible functional consequences of having it," says Robinson of his 15-year collaboration with Fahrbach.

A Powerful Marriage

Also in the 1990s, Robinson launched a new line of research to find which genes were active in the bee brain and might be involved in division of labor. Without the resources of genomics, however, he had to use the candidate gene approach, which essentially involved an educated guess. Robinson first targeted the *period* gene, which in fruit flies has several functions related to timing. "It was first identified for its role in regulating circadian rhythms," says Robinson, "but later work showed it also affected temporal processes at other time scales. In one direction, it affects wing beat frequency on the millisecond time scale, and then in the other direction, the duration of the preadult developmental period, a time scale measured in days." Because the transition from hive worker to forager in bees was an issue of timing, the *period* gene was a candidate for study.

Admittedly, this rationale seemed flimsy to Robinson, so he set out to strengthen it. Forager bees, which navigate and collect pollen based on both daily and seasonal patterns, were known to have strong circadian rhythms. But what about young bees, cloistered in a dark hive and working essentially around the clock? "There could be one of two possibilities," says Robinson. "Either the colony operates as a factory where each individual bee is rhythmic but they work different shifts, or there is more of an 'undergraduate' model, where the bees work and rest randomly with respect to the 24-hour day." With the help of a bunch of energetic human undergraduates, Robinson marked specific bees and monitored them around the clock, finding that the "undergraduate" model held true, and young bees were arrhythmic in their work behavior (10). However, as they matured, the bees developed more noticeable biological rhythms.

These findings provided enough of a connection to begin cloning the honey bee *period* gene, and subsequently Robinson found that changes in the regulation of the *period* gene were associated with changes in behavior, providing a connection between chronobiology and division of labor (11). However, the work itself was fairly arduous, requiring cloning the gene from scratch and pooling multiple brain samples for assays, not to mention the hassles of studying bees in the field. "I was worried that molecular biology and social behavior were not a particularly great match," Robinson says. In 1996, he went on sabbatical at Hebrew University in Jerusalem, hosted by Hermona Soreq, to improve his knowledge of molecular neurobiology. During his sabbatical, he came across a paper from Patrick O. Brown's laboratory on microarrays (12) and first started learning about genomics. "OK," Robinson thought, "this is the marriage that needs to be made—genomics and social behavior."

After consulting with genomics experts such as Leroy Hood and Jerry Rubin, Robinson decided the first step would be to create an expressed sequence tag (EST) database from the brains of bees. The only obstacle was that funding groups were not necessarily as enthusiastic about the marriage of genomics and behavior as Robinson was. "At that time, the honey bee was not considered a model organism for genomics and so was not eligible to receive genomic-specific funding," he says, "but an EST project is not hypothesis driven, and that would make it difficult to compete against more traditional and focused proposals for NIH or NSF funding. I guess I was caught betwixt and between." Fortunately, Robinson found an on-campus program called Critical Research Initiatives, which provided seed money to start his project and led to a Burroughs Wellcome fellowship, which helped him complete the ESTs.

"Of course, once you have a taste for the power of genomics, you want more," says Robinson, who then began thinking about sequencing the complete honey bee genome. In 2000, he held a meeting with other members of the bee community in Bellaggio, Italy, to explore this idea. Over the next couple of years, additional meetings and research findings helped build momentum. Robinson and his colleagues submitted their sequencing proposal "white paper" to the National Human Genome Research Institute in February 2002. The project was approved, and sequencing began at the Human Genome Sequencing Center at Baylor College of Medicine (Houston, TX) in December 2002. This groundbreaking work has been completed recently (13), adding the first genome from a social insect to the growing collection of organismal genomes.

Socially Responsible Behavior

Changes come quickly in science, and even as the last few bases of the honey bee genome came off the machine, Robinson began thinking about the future. The National Institutes of Health (NIH, Bethesda, MD) put out a call for the development of faster and cheaper sequencing methods, oft-described as the "$1,000 human genome," ultimately to provide diagnostic sequences for medicine. "But if a $1,000 human genome is achieved, then for many insect species, we can get a complete genome sequence for under 100 bucks!" says Robinson. He believes that the advent of these inexpensive sequences could open up the field of sociogenomics. By comparing individual, colony, and species differences, Robinson hopes to elucidate the connections between genes, social behavior, and social evolution. "There are so many different species of social insects, some with strikingly similar societies though they evolved independently, and others with various levels of sociality, from solitary to advanced eusocial. To be able to study all of that natural variation in social organization with the tools of genomics is going to be fantastic," he says.

Robinson has begun work that may begin to answer some sociogenomic questions. In one of his first microarray studies, he found that 40% of the genes in the honey bee brain had altered expression in foragers and hive bees (14). In his PNAS Inaugural Article (1), Robinson dissects these changes into a causal context. He and his team found that changes in expression occurred in two primary trends. First, age-related changes occur over a bee's first 8 days of adult life as the brain matures. Then behavior-related changes ensue that precede the shift from hive worker to forager. These latter changes are interesting because they seem to be independent of the environment, as foragers restricted to the hive were virtually identical to those allowed to roam. By comparing two honey bee subspecies that differed in their age at onset of foraging, Robinson also found several candidate genes as regulators of this behavior.

Robinson is careful to ensure that his work on genetics and social behavior is developed and understood accurately. "It seems like the debate about nature and nurture continues to be very polarized," he says. Robinson thinks that the advent of genomics has provided a unifying paradigm for analyzing the influences of "nature and nurture" (15, 16). Invoking an old Spanish proverb, "the horns of behavior are on the same bull," Robinson proposes that a new way to view nature and nurture is as hereditary and environmental influences on the genome that influence gene activity. He believes that gene expression has become the first phenotype of sociogenomics, and microarrays can become powerful measuring tools for it. "When you look at gene expression data, you see genes turning on and genes turning off. You see the dynamic nature of brain activity," Robinson says, "and you see the dynamic nature of behavior. It really captures the flavor of the genetic basis of behavior, which is not as deterministic as some may have thought previously."

Nick Zagorski, *Science Writer*

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